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Viral Hepatitis and the Public Health*

ALBERT M. SNELL,† M.D., *Rochester, Minnesota*

THE sporadic type of what is usually known as acute catarrhal jaundice has for years been the type of liver disease most commonly seen in hospital and general practice. Since the patients were usually young and recovered promptly and since the lesion was generally believed to be "duodenal catarrh" with a "mucous plug" in the ampulla of Vater, little serious thought was given to the condition. The occasional patient whose illness was protracted or who succumbed to the disease was regarded as having another ailment variously known as acute or subacute atrophy or nodular ("toxic") cirrhosis. Not infrequently, the most serious types of the disorder were regarded as examples of Weil's disease.

From time to time, various authors have called attention to the fact that the so-called catarrhal jaundice (Jones and Minot, 1923) was of some importance, that it was increasing in frequency and, at times, in severity, and that there might be residua which were pathologically significant. Virchow's conception of the pathologic lesion was challenged more than 50 years ago by Flindt, and about 20 years later Eppinger gave it the coup de grâce by demonstrating that a diffuse hepatitis was present. In spite of these interpretations of the disease, acute epidemic or sporadic hepatitis was not a subject to compel the attention of medical audiences until about five years ago, when hepatitis occurred in a large number of service personnel who had been inoculated with yellow fever vaccine. This experience was not entirely new, since Fox and his associates had encountered similar difficulties in Brazil, but it served as an impetus to a large number of investigative studies which have changed our conception of this supposedly innocuous ailment and have given it the status of a public health problem of first importance.

It is the purpose of this paper to point out that the disease appears to be increasing in frequency and probably in severity, that it may and often does lead to serious hepatic damage which may be progressive and eventually fatal, and that the present widespread use of blood, blood products and parenteral therapy may serve to disseminate the disease even more widely. Finally, it is hoped that a tentative explanation of some hitherto obscure types of chronic diseases of the liver may be advanced on the basis of these newly acquired facts.

HISTORICAL DATA REGARDING EPIDEMICS

The disease seems to have been mentioned by Hippocrates and has probably occurred during every war since the time of Homer. There is a record of correspondence between Pope Zachariah and St. Boniface, in the Eighth Century, concerning an epidemic of jaundice (Hardy and Feemster). Among the earlier epidemics on record are two which occurred in the Mediterranean area (Minorca, 1745; Ligurian coast, 1793) where the disease seems to be perennially active. Following the tradition of being "an old and ugly camp follower," the disease was widely prevalent in the Franco-Prussian War and in the Boer War. There are references to these earlier epidemics in the reports by Fröhlich and Cockayne. In more recent times, epidemics have occurred in the Eastern Mediterranean area in Russia [65] and in the Scandinavian countries, the epidemic of 1927 being especially widespread. The Scandinavian literature contains a graphic account of some of these outbreaks.[7, 10, 21, 80]

The first American epidemic occurred at Norfolk in 1812, according to Blumer, whose account of the spread of the disease in this country is noteworthy.

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† Division of Medicine, Mayo Clinic, Rochester, Minnesota.

Important for the historically minded is Woodward's account of the disease in the Union armies during the Civil War, when there were more than 52,000 cases and 226 deaths, a mortality rate of about 0.4 per cent. In World War I, American forces were not seriously affected but epidemics of various sizes continued through and after the war years in this country. An increase in acute yellow atrophy of the liver was noted following World War I (Berglund).

The British forces suffered severely from epidemic jaundice in the Dardanelles campaign of World War I; Willcox reported 4,000 cases and a mortality of 0.4 per cent. British forces in the Mediterranean area were again affected in World War II.[49] The disease began with an epidemic in the beleaguered garrison at Malta (1941-1943).[16] By the time American forces entered the war, the stage was prepared for an outbreak of pandemic proportions. As is well known, there were outbreaks in North Africa, Italy, on the European continent[77] and in the South Pacific Islands. More than 200,000 men had the fully developed disease and many more who suffered from it either did not report sick for various reasons or had the anicteric variety of hepatitis.

The spread of the disease since the war is difficult to appraise since the disease is not reportable in most states. Word of mouth information seems to indicate that its high incidence has continued, and in some states where it is reportable this impression is partially supported by figures.

The mortality in these epidemics deserves especial comment. As Cockayne pointed out years ago, there seems to be a correlation between epidemics of hepatitis and the occurrence of increasing numbers of cases of acute yellow atrophy. The connection was borne out in the Swedish epidemic of 1927[7] and recent figures from Denmark, notably those of Alsted and of Jersild, indicate a high incidence of acute and subacute atrophy during the years 1943-1945 inclusive. The mortality of the epidemic disease is in general due to hepatic necrosis, no matter what term may have been used to describe the disease (Lucké and Mallory). Incidentally, the increased mortality in recent years is reflected in figures from Palestine[12, 41] where the death rate is currently about three to six times that usually reported, a circumstance which may reflect crowding and bad sanitary conditions in that country.

ETIOLOGY

For some time past, especially since the studies of Findlay and MacCallum appeared (1937 and 1938), it has been suspected that the etiologic agent of hepatitis had the principal characteristics of a virus. This view is now supported by abundant evidence, although a virus has never been actually demonstrated, cultured, or grown on natural or artificial media. Two viruses and quite possibly more than one strain of each probably are involved. These two viruses have many features in common but differ in two ways; namely, the length of the incubation periods and their mutual failure to confer a heterologous immunity against infection by the other strain.[32, 33, 61] Before discussing the differences, it may be well to consider the characteristics which they share. They have not been seen with the electron microscope and they have not been successfully transmitted to any animal except man, in spite of extensive trials. There is some evidence, not generally accepted, to indicate that swine have been experimentally infected (Andersen). Neither strain can be detected by any specific laboratory method now available; only development of the disease after inoculation of a human being proves the presence of the icterogenic agent, a fact which has confined the study of these viruses to such observations as could be made on human volunteers.

Both viruses will pass through a Seitz filter and other filters which will retain bacteria. They are among the most resistant pathogens. They are able to withstand freezing, exposure to a temperature of 56° C. for 30 to 60 minutes and long storage in the desiccated state at room temperature. They are not killed by a 1:2,000 solution of merthiolate, by a 0.5 per cent solution of phenol in ether or by a 0.2 per cent solution of tricresol. The ordinary type of water chlorination does not affect them. They may be inactivated by autoclaving, by boiling or by exposure to ultraviolet light.

The essential differences in their behavior are shown in Table I. For the purposes of the consideration to follow, Neefe's[58] nomenclature will be used

TABLE 1.—*Differences Between Infectious and Serum Hepatitis* *

	Infectious Hepatitis	Serum Hepatitis
Fever	+	Rare
Incubation period	20-45 da.	60-150 da.
Transmission by ingested feces	+	—(?)
Parenteral transmission	+	+
Homologous immunity	+ (1 yr. +)	+(18 mo. +)
Heterologous immunity	—	—
Mortality rate	0.01 to 0.20	0.2 to 20.0%
Morbidity, relapses	++	++

* Modified from Neefe, J. R., Stokes, J. R., and Gillis, S. S.: Hepatitis; immunologic studies, Tr. A. Am. Physicians, 59:142, 1946.

and these viruses will be referred to as virus IH (infectious hepatitis, the naturally occurring disease) and virus SH (serum hepatitis, the artificially transmitted form). For a full consideration of these agents and the data on which differentiation is made, the reader is referred to Neefe's[58] excellent review. Only three additional points of clinical interest will be stressed: (1) virus IH may be transmitted by both enteral and parenteral routes, while virus SH has to date been transmitted only parenterally; (2) the period of viremia extends through much of the long incubation period of virus SH, while it is relatively brief with virus IH, and (3) the pathologic lesions induced by either virus seem to be more or less identical but the over-all mortality due to infection with virus SH is considerably greater.

MODES OF TRANSMISSION

As indicated previously, these viruses are extraordinarily resistant to a wide variety of agents and may be transmitted by various means. The naturally occurring disease dependent on virus IH is probably transmitted by the "intestinal-oral" circuit in most instances. It is most readily propagated in areas where there is crowding and poor sanitation, and direct personal contact seems epidemiologically important. The ordinary epidemic in civilian communities pursues a leisurely course over a period of three or four months;[55, 62] whole families may be affected, the members becoming ill one at a time at fairly regular intervals. In a military command in the field, the spread of the infection may be greatly accelerated.[49] Infection by contaminated water certainly occurs, and if so, many persons will contract the disease simultaneously, as in the Pocono camp epidemic which was carefully studied by Neefe and Stokes. Dissemination by droplet infection is believed to occur;[15] there is also a suggestion that the disease may be spread by food or fomites. The field incidence of the disease is high among military officers who often share china and silver in a mess.[44, 81] Kirk, on the basis of his experience in North Africa, expressed the opinion that flies contaminated by human excreta might spread the disease. It has also been felt that the possibility of transmission by biting insects can not be excluded.

The percentage of persons affected in a community in which epidemic hepatitis is present varies tremendously. The age factor may be important; children and young adults are especially susceptible and there is evidence to suggest some degree of immunity in many persons more than 30 years of age. With contaminated water, mass infection may be the rule (65 per cent in the Pocono camp epidemic). In military personnel in the field, an incidence of 40 to 50 per cent is not uncommon. In some American epidemics cited by Blumer, with normal civilian surroundings and a mixed population, the rates of incidence ranged from 5 to 67 per 1,000. How often the virus IH is transmitted by parenteral means remains unknown; that this may occur is well known, as in the disastrous occurrence cited by Murphy.

The transmission of the SH virus is so well illustrated by the familiar story of the incidents which followed yellow fever vaccination that further amplification seems unnecessary.[35, 79] Contaminated human serum transmitted the virus in this instance. There are some recently reported aspects of the matter which merit some consideration. The first has to do with the rates of incidence when large groups are inadvertently inoculated with material containing virus SH. There is an unpublished report of one recent episode in which a large number of men were inoculated in this manner. Frank hepatitis developed in 49 per cent of the men and 27 per cent had evidence of hepatitis without icterus (established on the basis of hepatic functional tests). Other authors have reported about the same incidence in dealing with smaller groups of persons who were inoculated in this manner.

The second aspect has to do with the matter of accidental inoculation by contaminated syringes and needles and concerns the incidence of jaundice in patients subjected to repeated "sticking" for obtaining samples of venous and capillary blood. In one Scandinavian city, it has been reported that about 80 per cent of all instances of hepatitis occurred in persons who had been in hospitals for various reasons and that the rate of occurrence was in rough proportion to the number of acupuncture venipunctures performed. Among diabetic patients, for instance, the incidence of the disease is extremely high. Selander previously noted this high incidence in diabetic patients and there are, of course, numerous reports of instances of infection in diabetic[19] and chrysotherapy clinics.

Finally, the earlier reports on the relation of jaundice to arsenotherapy for syphilis should be mentioned. Only three of the many reports will be considered. That of Ruge, from the German Navy, indicated that in about one of every three cases jaundice had been preceded by arsphenamine therapy. This fact and a progressively rising annual rate of "arsenical jaundice" which he reported would be interpreted today as probably indicating the dissemination of virus SH by contaminated syringes. The report of Stokes and his associates shows the variability of supposed arsenical hepatitis under conditions which exclude practically all variables except the dissemination of hepatitis virus in the manner mentioned. In at least one British clinic[69] where arsphenamine jaundice was a common development during the second or third month of treatment of syphilis, the jaundice disappeared when individual syringes were substituted for the original multiple injection technic. The importance of the accidental transmission of hepatitis by syringes has recently been the subject of a report by the British Ministry of Health.[53] It is now known that bacteria may survive the usual cleansing and sterilizing procedures employed in many clinics and that the much more resistant virus can do so seems certain. Whether the virus transmitted is of the IH or SH type probably makes relatively little difference; the fact remains that the mechanics of present day medicine and the current use of blood and blood products furnish the greatest possible opportunity for the propagation of hepatitis virus. The long period of viremia for virus SH obviously makes it more likely to be transmitted by artificial means. The frequency of the artificial type of transmission of the disease has been verified by many observers[5, 17, 73] and I know of dozens of instances of this so-called homologous serum hepatitis, some of which have been described elsewhere in connection with hepatitis in wounded men.[74]

Serum hepatitis has been observed after the use of measles[50] and mumps convalescent serum, whole blood, pooled plasma, both liquid and dried, and both yellow fever and pappataci fever vaccine contaminated with icterogenic serum. It has an appreciable mortality, as high as 20 per cent in some series. Middleton mentioned a group of cases observed in the European war front in which the mor-

tality rate was 9.5 per cent. These high mortality rates may reflect in part the condition of the patients (often injured or wounded men) rather than the natural virulence of different strains of virus. The size of the inoculum appears to make little or no difference, since serious hepatitis has followed the administration of 0.01 cc. of the icterogenic agent while much larger doses appear to have produced a hepatitis of no more than the ordinary degree of severity.

While plasma is the commonest means of transmission, whole blood may be solely responsible for transmitting the disease. Bradley's figures from the Emergency Medical Service of Great Britain showed that, for instance, the incidence of jaundice was one hundred times higher in transfused casualties than in those not so treated. At one time, homologous serum jaundice following the use of blood or plasma was the commonest cause of death in the United States army hospitals in England, accidents and pneumonia excepted. So well established has this method of transmitting the disease become that one is inclined to agree with Bradley in the following statement: "When hepatitis occurs 40 to 120 days after the administration of a human blood product or other parenteral therapy, it is almost certainly homologous serum jaundice and must be treated as a disease with an appreciable mortality." The implications in the field of diagnosis and in the selection of jaundiced patients for surgical exploration are obvious. On one gastro-intestinal service of which I have knowledge, eight patients who had homologous serum jaundice were admitted with a presumptive diagnosis of obstruction of the common bile duct or a malignant lesion within the past three months. Schiff has recently commented on this fact and has pointed out the dangers involved.

IMMUNOLOGY

There seems to be a gradually decreasing susceptibility to the naturally occurring disease (virus IH) which develops with age. This is believed to be due to the fact that this virus is sufficiently widespread to immunize most of the population by apparent or subclinical infection during the earlier years of life. The experimentally produced disease in human volunteers confers immunity to subsequent inoculation with the homologous virus for at least a year. There is also an antigenic relation between virus IH strains isolated from cases in widely separated parts of the world, but heterologous immunity to virus SH does not develop.[58] Second attacks of the naturally occurring disease are certainly no more common than second attacks of measles or mumps. Finally, from pools of adult human serum, gamma globulin can be prepared which contains antibodies effective against virus IH and possibly also against virus SH infections.

Little is known about immunity to the latter virus, except that which has been learned by studies on volunteers. One attack confers immunity for 18 months at least. As stated previously, no cross immunity between the two viruses has been demonstrated and certainly there is no increasing immunity to SH virus with age, as is the case with virus IH. There is in fact some evidence to suggest that a previous attack of serum hepatitis renders a person somewhat more susceptible than normal to the naturally occurring disease, whereas the reverse is not necessarily true.[58]

The question also arises as to when and where the serum hepatitis virus originated since the disease appears to be propagated only by artificial means. Neefe[58] has stated that certain persons may at times carry the agent in their blood without ever having had clinical or laboratory signs of hepatitis; this fact has been established by a study of donors to plasma pools which were shown to contain the icterogenic agent. Whether or not the virus of serum hepatitis is a variant of IH virus changed by prolonged adaptation to a human host can only be surmised; the matter of some interrelation is suggested by the sudden appearance of serum hepatitis during a time when the incidence of the naturally occurring disease was increasing markedly. The survival of virus in immune persons and in other persons who have the various lesser residua of hepatitis is a matter of great importance. There is to date no information on any possible animal reservoir of the disease, as is the case with other virus infections. Like amebiasis, the disease appears to be transmitted only from man to man and one must, it seems, postulate both the existence of a human reservoir and the probability of a carrier state. Furthermore, one finds it difficult to explain the phenomena that have just been described unless the reservoir is large and the carrier state is a relatively common occurrence. The matter will remain unsettled until some suitable experimental medium can be found for the propagation of the disease.

CLINICAL COMMENTS ON VIRUS HEPATITIS

The clinical manifestations of both virus and serum hepatitis have been described many times both under their proper titles and as "epidemic" or "catarrhal" jaundice. Only a few less generally appreciated aspects will be considered here. There is a considerable variation in the clinical picture in various epidemics in cases which occur sporadically,[43] and in the severity of individual cases in epidemics.[31] Cervical adenopathy and the appearance of abnormal lymphocytes in the blood have been described in some epidemics but not in others; in some outbreaks, neurologic symptoms have been conspicuous (Lyon; Stokes, Owen and Holmes; Byrne and Taylor). There are records of some highly fatal outbreaks (Sandwith, 1904; Tillgren, 1928) and some with an unusually large incidence of residual atrophy of the liver, both acute and subacute (Alsted, 1947; Jersild, 1945). The coexistence of hepatitis with other infectious diseases (notably malaria and dysenteries due to Salmonella) greatly modifies the clinical course of the disease in the direction of increased morbidity and late relapse. The disease is a much more serious affair in pregnant women and the mortality under these circum-

stances is high, a point on which observers all over the world agree. Mortality rates in various epidemics range from a negligible figure through the average of about 0.2 per cent to 2 per cent or more. These variable features suggest the existence of more than one strain of virus.

The existence of cases of anicteric hepatitis has been fully established; as previously stated, this type of the disease is important epidemiologically and, since it may escape early clinical recognition, it may lead to prolonged illness and permanent hepatic injury. Relapses are extremely important and frequent; they may be clinical or "serologic" only, and as Barker, Capps and Allen have shown, are often precipitated by early resumption of physical activity, by the use of alcohol or by intercurrent infection. I have observed several cases in which jaundice has persisted intermittently over a period of several months before the patients finally recovered.

A word must be said here in regard to liver function tests, which are very important in the recognition of the anicteric type of the disease and of relapses and recrudescence. These appear in a fairly regular order at the onset of the disease and disappear in a roughly inverse order during convalescence (Neefe[59]). The tests which are most likely to remain positive long after the disease has passed are those which have to do with alterations in the plasma proteins; namely, the thymol turbidity test and other flocculation tests. Further reference to these tests will be made in considering means of diagnosing the residua of the disease. The significance of persistently positive flocculation tests has been confirmed by biopsy. Microscopic examination of material obtained by needle puncture may reveal active hepatitis six or nine months after all tests for hepatic function become normal.[57]

Finally, some reference must be made to the recorded disturbances in hepatic physiology incidental to either virus or serum hepatitis. These often are severe, if not as permanent, as those seen in cases of cirrhosis. Among those worthy of mention are: (1) disturbed excretory function for the products of hemoglobin disintegration and for certain dyes, (2) a decrease in the concentration of serum albumin, reversal of the albumin-globulin ratio and a change in the electrophoretic pattern,[52] (3) hypoglycemia associated with symptoms referable to the central nervous system, (4) a prothrombin deficit uncorrectable by the administration of naphthoquinone (vitamin K), (5) failure of synthesis of urea and hippuric acid, (6) retention of estrogenic material normally inactivated by the liver (Gilder and Hoagland), (7) disturbances of lipid metabolism and (8) the appearance and disappearance of vascular spiders. In most instances, these changes are of a temporary nature but they reveal clearly the extent of the hepatic injury. Even the retention of water in body tissues, which is characteristic of atrophic cirrhosis, is duplicated on a considerable scale. During active epidemic hepatitis there are evidence of gross retention of water and chloride in interstitial tissue spaces and indications of diuresis and restoration of the normal amount of tissue fluid during recovery (Labby and Hoagland). This phenomenon is believed to be due to the temporary inability of the liver to inactivate antidiuretic substances formed in the hypophysis.

RESIDUA OF VIRUS HEPATITIS

The residua of virus hepatitis are not completely catalogued in spite of the extensive experience of the last few years, yet enough is known to indicate that many supposedly independent hepatic diseases originate in what was to all intents and purposes an attack of virus hepatitis. Until an experimental animal is available to which the disease can be transferred, some of these supposed etiologic relations must remain on a tentative basis.

It should be emphasized that complete healing of the hepatic lesion is the rule in the great majority of cases. Lucké's studies,[45, 46] which were based on biopsy and necropsy, established this point beyond question and the studies of Roholm and Iversen and of Dible and his associates are, in general, confirmatory.

The cases in which healing does not occur may be divided into four groups: (1) cases in which fulminant hepatitis (acute atrophy) develops; (2) cases in which chronic atrophy or "nodular cirrhosis" develops (3) cases in which a cholangiolitic type of cirrhosis develops, and (4) cases in which minor residua occur. These groups will be considered separately.

Fulminant Hepatitis:

This condition may be described as a fatal form of the disease which pursues its entire course within ten days. Clinically, the condition corresponds to the often described acute yellow atrophy of the liver with which it is probably identical; certainly there are no important clinical or pathologic differences. It is of interest to note that other epidemics in the past have been said to have been associated with a notable increase in the occurrence of this fulminating type of the disease (Ehrstrom, Bergstrand, Bormann). Other authors do not agree that such a correlation exists (Selander). However, the death rate from this cause has risen in this country in recent years[20] (Figure 1).

In cases of this type of the disease, the most striking features are the rapid development of severe hepatic insufficiency, often attended by neurologic findings of great variety, rarely by hypoglycemic convulsive seizures and not infrequently by a hemorrhagic diathesis. At necropsy, the principal findings are those which pertain to the liver; examination of this organ shows an extensive and widespread necrosis of the lobules and complete disintegration of the cellular structure. Lucké and Mallory have described the experience of the United States Army with this condition in the period between August, 1943, and April, 1945. In this period there were 196 deaths from epidemic jaundice; in 53 per cent of the 196 cases in which death occurred, the disease was of the fulminant type. These authors noted that not a single case of fulminant hepatitis was reported

during the 1942 epidemic of hepatitis which followed yellow fever inoculation. In more than half of the cases of fatal fulminant hepatitis which they reported, the disease apparently was due to the transmission of the virus by parenteral means. A number of explanations for the sudden increase in the incidence of fulminant hepatitis have been suggested. A difference in virus strains may be considered or there may be an increase in the virulence of the virus as a result of repeated human passage. Host factors are possibly important since many of the victims had been subjected to the rigors of combat or to other abnormal living conditions.

Chronic Atrophy (Coarsely Nodular Cirrhosis):

In most reports of large series of cases of epidemic hepatitis, reference is made to the occurrence of protracted illness which terminates with the clinical picture of portal cirrhosis after a variable time. This type of the disease affects persons of all ages and of both sexes. The pathologic picture is quite characteristic; whole lobules of the liver may be destroyed and leave only the connective tissue framework, while other areas may be the site of coarse nodular regeneration. The structure of the liver is grossly disorganized and distorted, which produces the condition which Mallory designated as "toxic cirrhosis." [51] The bromsulfalein test for liver function discloses a marked retention of the dye. The cephalin cholesterol test and the thymol turbidity test are positive. The prothrombin time increases, and the values for cholesterol and cholesterol esters decrease progressively.

Recent reports from Scandinavian countries indicate that the incidence of this progressively destructive hepatitis is high among women who are past the menopause (Jersild, Alsted). The reason for this is obscure. I have observed several cases of coarsely nodular cirrhosis in which the patients were young males.

The disease appears to be progressive in spite of treatment and the outcome usually is unfavorable.

Chronic Hepatitis Associated with Jaundice ("Cholangiolitic Cirrhosis"):

The literature contains reports of cases in which a prolonged jaundice with remarkable preservation of the essential functions of the liver has followed in the wake of what was supposedly an ordinary form of infectious hepatitis. In these cases the disease resembled the hypertrophic biliary cirrhosis described by Hanot, a classification which has become a sort of catchall for all types of chronic unexplained jaundice. The profession is indebted to Watson, Hoffbauer and Howard for clarifying this subject and for their description of what they termed "cholangiolitic cirrhosis," a very gradually progressive form of hepatitis characterized by the phenomena usually associated with regurgitation jaundice (hyperbilirubinemia, hyperphosphatasemia, hypercholesterolemia) and well-preserved metabolic function. Liver biopsy revealed a progression from mild hepatitis to advanced portal cirrhosis; in Case 10 of their series, this process continued over a period of 33 years and death finally occurred as a result of hemorrhage from esophageal varices. Chester Jones has mentioned a similar experience. In each instance, a member of the patient's family had jaundice at about the same time as the patient did; the jaundice in the member of the family had disappeared while the patient's illness had become progressive and permanent. There are undoubtedly many similar cases not as yet recorded but the relation of the disease to infectious hepatitis rests as yet on purely circumstantial evidence.

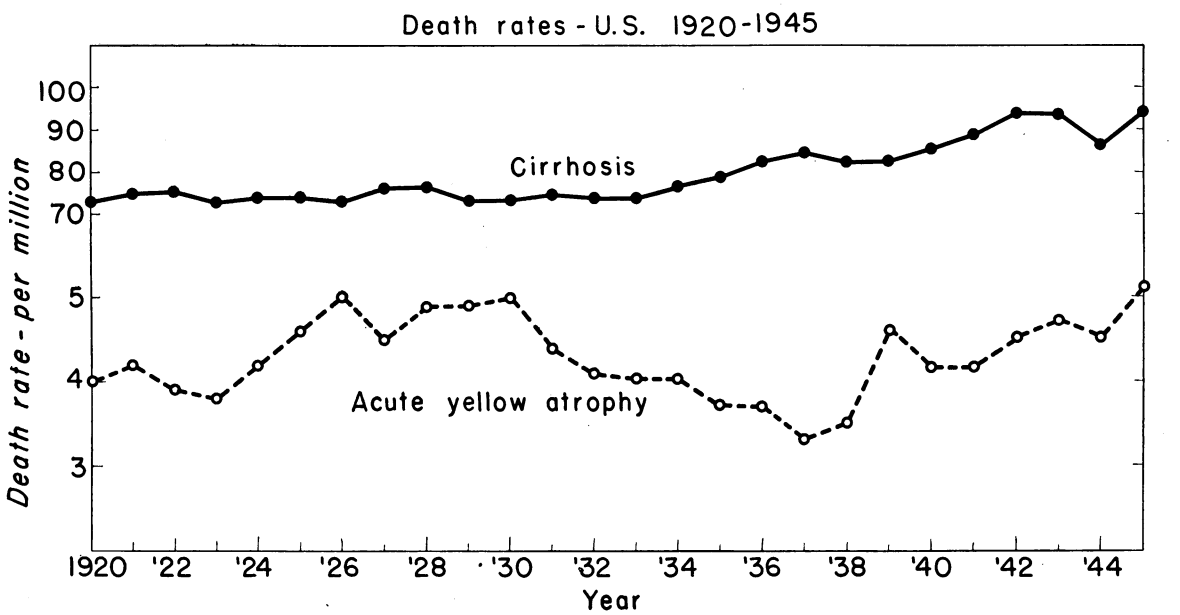

Figure 1.—Death rates from cirrhosis of the liver and from acute yellow atrophy in the United States, 1925 through 1945.

Minor Residua:

The minor residua of hepatitis are so designated here merely to distinguish them from the serious and progressive conditions previously mentioned. The existence of residual hepatomegaly and disturbances of hepatic function has been known for years (Polack, Rennie, Altschule and Gilligan) but not much clinical significance was attached to them (in spite of Bloomfield's suggestions as to their possible relation to a later cirrhosis) until Barker and his associates rediscovered the disease in the Mediterranean theater of war. It is a matter of common knowledge that there are many persons who bear the anatomic and physiologic scars of hepatitis (both IH and SH types) incurred during the recent war, and follow-up studies in such cases constitute a major medical problem for this generation of physicians and the next. Both active and inactive forms of chronic hepatitis undoubtedly exist. What their eventual outcome will be can only be surmised. I am inclined to share the views of Klatskin and Rappaport, who found clinical and laboratory evidence of residua in about half of a series of cases seen from a few months to 27 years after an acute episode of hepatitis but who did not feel that their findings were necessarily indicative of the development of progressive damage of the liver. A number of reviews of such cases will be made in the near future and until a large and statistically significant sample of late World War II hepatitis is studied the matter is best left undecided.

PREVENTION AND CONTROL

The excreta of patients with active infectious hepatitis should obviously be handled in the same manner as are those of typhoid patients, in spite of the fact that the length of time the feces contain the virus is not known. Considerable care should be exercised in regard to the handling of syringes and needles used in obtaining specimens of blood from, or in giving intravenous infusions to, such patients; they should be boiled or autoclaved before being used for other purposes. Particularly during epidemics, all possible precautions should be taken to avoid contamination of food, water and milk. Screening should be practiced to exclude transmission of the disease by insects.

Passive protection of persons exposed to the naturally occurring disease may be furnished by the administration of human gamma globulin (Gellis, Stokes and others, and Havens and Paul). The material is not available as yet for large scale general use, but it may be advisable to employ it in the protection of pregnant women or exposed persons in whom the disease might carry an unusual risk.

The protection of the community against serum hepatitis is a complex and difficult problem, particularly so since it is impossible to detect the virus of the disease in the blood of prospective donors by any means now available. Exclusion of persons, in whom hepatitis may be developing or who have just recovered from it, by some simple tests, such as the modified Harrison spot test for bilirubin or one of the flocculation tests, should be considered. Obviously, donors of blood should also be questioned carefully regarding any previous history of illness. Unfortunately, persons who have epidemic hepatitis without jaundice as well as persons who have to all intents and purposes never been ill may be carriers of the icterogenic agent (virus SH). Against this phenomenon, all precautions seem likely to be useless. Suggestions have been made as to the size of the pool of blood from which plasma is made. Very large pools would, of course, tend to dilute the icterogenic agent, but in view of the extremely small amounts required to transmit the disease, this approach does not appear entirely practical. Such large pools may all provide some protective antibodies against the disease. Small pools would, of course, tend to reduce the mathematical chances of transmission. Treatment of the plasma with ultraviolet light has been suggested by Oliphant and Hollaender, and this method seems to have promise. The plasma proteins may be altered somewhat by this treatment but there is no evidence of damage to antiviral and antibacterial substances. Passive prevention is still in the experimental stage. The importance of maintaining a diet high in protein and sources of vitamin B complex in ill or injured patients receiving transfusions of plasma is obvious. The use of gamma globulin as a possible preventive measure against virus SH infection is still under investigation. There are some recorded observations which seem to indicate that two 10 cc. doses administered about a month apart furnish a considerable degree of protection against homologous serum jaundice, but further confirmatory evidence is needed to establish the value of the procedure. In cases in which the disease develops after such treatment it does so only after a very long incubation period and the disease is said to have been mild.

For the present, and until such time as prospective carriers of the SH virus can be eliminated or the virus inactivated by some means, the most satisfactory plan will be to limit the use of blood, and particularly plasma, to cases in which the necessity outweighs the risk. When possible, plasma should be followed by two 10 cc. doses of gamma globulin at monthly intervals until a better means of prevention is available.

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